Research tool

L2 ANSWER 1 OF 8 MEDLINE
AN 2002387735 MEDLINE
DN 22131739 PubMed ID: 12135781
TI Secreted Reelin molecules form homodimers.
AU Kubo Ken-ichiro; Mikoshiba Katsuhiko; Nakajima Kazunori
CS Department of Molecular Neurobiology, Institute of DNA Medicine, Jikei University School of Medicine, 3-25-8 Nishi-shinbashi, Minato-ku, Tokyo 105-8461, Japan.
SO NEUROSCIENCE RESEARCH, (2002 Aug) 43 (4) 381-8.
Journal code: 8500749. ISSN: 0168-0102.
CY Ireland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200210
ED Entered STN: 20020724
Last Updated on STN: 20021011
Entered Medline: 20021010
AB During mammalian brain development, neurons are generated along the ventricle, migrate radially, and become aligned in defined patterns. These precise patterns of neuronal alignment are regulated by an extracellular matrix protein Reelin, and binding of Reelin to its receptors induces tyrosine phosphorylation of the intracellular adaptor protein disabled 1 (Dab1). We recently reported that Reelin molecules assemble to form a homomeric protein complex. Although the number of molecules in the full-length complex is unknown, recombinant N-terminal fragments, which contain the **epitope** for the function-blocking **CR-50** antibody, assembled to form a complex of more than 40 monomers. When the N-terminus was deleted from Reelin, the truncated protein did not form a stable complex. To further characterize the Reelin assembly, we performed biochemical analysis of the full-length Reelin assembly in this study. Here, we report that a full-length Reelin forms a disulfide-linked homodimer. A chemical crosslinking experiment on secreted Reelin confirmed that only dimers are formed by the full-length protein. However, interestingly, chemical crosslinking of the N-terminus-truncated Reelin resulted in the formation of larger complexes, in addition to dimers, suggesting that the tertiary structure required for the proper and stable assembly/dimerization was altered by the truncation. The truncated protein did not induce efficient tyrosine phosphorylation of Dab1, although it bound well to the receptors. These findings demonstrate the functional importance of the N-terminal region of Reelin for proper dimerization and signaling. Proper but not simple extracellular crosslinking of the receptors by these dimers may be important for Reelin signaling to occur.

L2 ANSWER 2 OF 8 MEDLINE
AN 2000440067 MEDLINE
DN 20402603 PubMed ID: 10920200
TI Reelin molecules assemble together to form a large protein complex, which is inhibited by the function-blocking **CR-50** antibody.
AU Utsunomiya-Tate N; Kubo K; Tate S; Kainosho M; Katayama E; Nakajima K; Mikoshiba K
CS Laboratory for Developmental Neurobiology, Brain Science Institute, RIKEN, Wako, Saitama, Japan.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Aug 15) 97 (17) 9729-34.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Priority Journals
EM 200009
ED Entered STN: 20000928
Last Updated on STN: 20000928
Entered Medline: 20000919
AB Reelin is a key mediator of ordered neuronal alignment in the brain. Here, we demonstrate that Reelin molecules assemble with each other to form a huge protein complex both in vitro and in vivo. The Reelin-Reelin interaction clearly is inhibited by the function-blocking anti-Reelin antibody, **CR-50**, at a concentration known to inhibit Reelin function. This assembly is mediated by electrostatic interaction of the **CR-50 epitope** region. Recombinant **CR-50 epitope** fragments spontaneously constitute a soluble, string-like homopolymer with a regularly repeated structure composed of more than 40 monomers. Mutated Reelin, which lacks the **CR-50 epitope** region, cannot form a homopolymer and fails to induce efficient tyrosine phosphorylation of Disabled 1 (Dab1), which should occur to transduce the Reelin signal. These data suggest that Reelin exerts its biological function by composing a large protein assembly driven by the **CR-50 epitope** region, proposing a novel model of the Reelin signaling in neurodevelopment.

L2 ANSWER 3 OF 8 MEDLINE
AN 1999238022 MEDLINE
DN 99238022 PubMed ID: 10223511
TI A panel of monoclonal antibodies against reelin, the extracellular matrix protein defective in reeler mutant mice.
AU de Bergeyck V; Naerhuyzen B; Goffinet A M; Lambert de Rouvroit C
CS Department of Physiology, University of Namur Medical School, Belgium..
vinciane.debergeyck@fundp.ac.be
SO JOURNAL OF NEUROSCIENCE METHODS, (1998 Jul 1) 82 (1) 17-24.
Journal code: 7905558. ISSN: 0165-0270.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199907
ED Entered STN: 19990715
Last Updated on STN: 19990715
Entered Medline: 19990707
AB Reelin, the extracellular matrix protein defective in reeler mutant mice, plays a key role during brain development. We therefore raised antibodies directed against various reelin **epitopes** in order to facilitate biochemical and cell biological studies of this important molecule. Homozygous reeler mice with a large deletion of most of the reelin gene were immunized with fusion proteins and carrier-coupled peptides corresponding to parts of the reelin sequence. Monoclonal antibodies were produced using classical procedures, screened using ELISA and-or western blot prepared with the antigen, and tested by immunohistochemistry and immunoprecipitation assays to detect endogenous reelin. The labeling of Cajal-Retzius cells in the embryonic mouse telencephalon was selected as criterion for positivity in immunohistochemistry. A total of 11 monoclonal antibodies were obtained, providing useful additions to the widely used antibody **CR-50**. Five are directed against the N-terminal part of reelin, among which three recognize the region that has significant similarity with F-spondin, and two are specific for hinge region located downstream from the F-spondin similarity region and upstream from the reelin repeats. Six antibodies are directed against the C-terminal part of reelin, among which one anti-peptide antibody recognizes the highly basic C-terminal segment. Antibodies against the N-terminal region stain well in immunohistochemistry. By comparison, the

labeling of embryonic Cajal-Retzius cells with antibodies directed against the C-terminal region is weaker, suggesting that this part of the molecule might be modified or not be as readily accessible in the tissue as the N-terminus.

L2 ANSWER 4 OF 8 MEDLINE
AN 1998316252 MEDLINE
DN 98316252 PubMed ID: 9651544
TI Role of reelin in the control of brain development.
AU Curran T; D'Arcangelo G
CS Department of Developmental Neural Biology, St. Jude Children's Research Hospital, Memphis, TN 38105, USA.. fos1@aol.com
NC NS09698 (NINDS)
P30CA21765 (NCI)
RO1NS36558 (NINDS)
SO BRAIN RESEARCH. BRAIN RESEARCH REVIEWS, (1998 May) 26 (2-3) 285-94. Ref: 58
Journal code: 8908638. ISSN: 0165-0173.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199808
ED Entered STN: 19980910
Last Updated on STN: 19980910
Entered Medline: 19980828
AB Reeler is an autosomal recessive mutation in mice that results in widespread disruption of laminated regions of the brain. We isolated a gene, reelin, that is mutated in reeler mice. The protein product of reelin has features of extracellular matrix components and it is expressed in a temporal and spatial pattern during embryonic and postnatal development consistent with the phenotypic defects in reeler mice. To understand the molecular basis of the function of Reelin, we constructed a full length reelin clone and used it to direct Reelin expression. Using this clone we found that Reelin is a secreted glycoprotein and that a highly charged C-terminal region is essential for secretion. Furthermore, we demonstrated that an amino acid sequence present in the N-terminal region of Reelin contains an **epitope** that is recognized by the **CR-50** monoclonal antibody. **CR-50** was raised against an antigen expressed in normal mouse brain that is absent in reeler mice. The interaction of **CR-50** with its **epitope** has been shown to disrupt neuronal migration in vitro and in vivo. We used **CR-50** to precipitate p385 Reelin from reticulocyte extracts programmed with reelin mRNA, from cells transfected with reelin clones and from cerebellar explants. Reelin appears to function as an instructive signal in the regulation of cell patterning during development.

L2 ANSWER 5 OF 8 MEDLINE
AN 1998068756 MEDLINE
DN 98068756 PubMed ID: 9406921
TI A truncated Reelin protein is produced but not secreted in the 'Orleans' reeler mutation (Reln[rl-Orl]).
AU de Bergeyck V; Nakajima K; Lambert de Rouvroit C; Naerhuyzen B; Goffinet A M; Miyata T; Ogawa M; Mikoshiba K
CS Department of Physiology, FUNDP Medical School, Namur, Belgium.. vinciane.debergeyck@fundp.ac.be
SO BRAIN RESEARCH. MOLECULAR BRAIN RESEARCH, (1997 Oct 15) 50 (1-2) 85-90.
Journal code: 8908640. ISSN: 0169-328X.

CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199802
ED Entered STN: 19980226
Last Updated on STN: 19980226
Entered Medline: 19980219
AB Reelin is the protein defective in reeler mutant mice [I. Bar, C. Lambert de Rouvroit, I. Royaux, D.B. Krizman, C. Dernoncourt, D. Ruelle, M.C. Beckers, A.M. Goffinet, A YAC contig containing the reeler locus with preliminary characterization of candidate gene fragments, Genomics 26 (1995) 543-549; G. D'Arcangelo, G.G. Miao, S.C. Chen, H.D. Soares, J.I. Morgan, T. Curran, A protein related to extracellular matrix proteins deleted in the mouse mutant reeler, Nature 374 (1995) 719-723; S. Hirotsune, T. Takahara, N. Sasaki, K. Hirose, A. Yoshiki, T. Ohashi, M. Kusakabe, Y. Murakami, M. Muramatsu, S. Watanabe, K. Nakao, M. Katsuki, Y. Hayashizaki, The reeler gene encodes a protein with an EGF-like motif expressed by pioneer neurons, Nature Genet. 10 (1995) 77-83]. In the Orleans allele of reeler (symbol: Reln[rl-Orl]), a 220 nucleotide deletion is present in the 3' region of the Reelin message, resulting in a frame shift with production of a predicted protein amputated from its C-terminal amino acids. In this study, we first show that the predicted truncated protein indeed exists in Orleans reeler mice, using several anti-Reelin antibodies. Three antibodies are directed against **epitopes** located in the N-terminal region of the protein, namely: monoclonal antibody **CR-50** [M. Ogawa, T. Miyata, K. Nakajima, K. Yagyu, M. Seike, K. Ikenaka, H. Yamamoto, K. Mikoshiba, The reeler gene-associated antigen on Cajal-Retzius neurons is a crucial molecule for laminar organization of cortical neurons, Neuron 14 (1995) 899-912] (**epitope** region between Reelin residues 251-407), monoclonal antibody G10 (**epitope** located between amino acids 199 and 244) and the polyclonal antipeptide rp4 (positions 381-399). A fourth antibody, antipeptide rp5, reacts with the C-terminal (3443-3461) Reelin sequence. In normal embryos, all four antibodies stained cells in the marginal zone with features of Cajal-Retzius cells. While N-terminal specific antibodies detected Reelin immunoreactivity in mouse embryos homozygous for the reeler-Orleans mutation, no staining was obtained with the rp5 antibody, showing the presence of a truncated protein. Moreover, although Reelin could be detected at the surface of living Cajal-Retzius cells of normal mice, it was not revealed after vital staining of embryonic cortex from Orleans reeler mice. These results indicate that the C-terminal region of Reelin is essential for its secretion and suggest that the Orleans reeler phenotype is due to defective Reelin secretion rather than to secretion of an inactive protein.

L2 ANSWER 6 OF 8 MEDLINE
AN 97465860 MEDLINE
DN 97465860 PubMed ID: 9321693
TI Dual role of Cajal-Retzius cells and reelin in cortical development.
AU Frotscher M
CS Anatomisches Institut der Albert-Ludwigs-Universitat Freiburg, Postfach 111, D-79001 Freiburg, Germany.. frotsch@sun2.ruf.uni-freiburg.de
SO CELL AND TISSUE RESEARCH, (1997 Nov) 290 (2) 315-22. Ref: 45
Journal code: 0417625. ISSN: 0302-766X.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199711

ED Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971118

AB Cajal-Retzius (CR) cells are transient neurons located in the marginal zones of the neocortex and hippocampus. Recent studies have shown that they synthesize and secrete the glycoprotein reelin. This extracellular matrix protein has sequence similarities with cell adhesion molecules and other extracellular matrix proteins, such as tenascin and laminin, suggesting a role in cell migration and process outgrowth. In reeler mutant mice lacking reelin, the orderly inside-out deposition of neocortical cells during development is disturbed, indicating that reelin is essential for normal cortical lamination. In the hippocampus, CR cells and reelin have recently been found to be important for the normal lamina-specific fiber ingrowth of afferents from the entorhinal cortex. These fibers are known to terminate in superficial layers of the hippocampus and dentate gyrus, regions in which CR cells are located. Both selective elimination of CR cells by local lesions and antibody blockade (**CR-50** antibody) of an important **epitope** near the N-terminus of reelin result in severe alterations of the growth of entorhinal axons in co-cultures of the entorhinal cortex and hippocampus. It is hypothesized in this review that reelin functions as a stop signal for both migrating neurons and growing fibers in the developing central nervous system.

L2 ANSWER 7 OF 8 MEDLINE
AN 97368343 MEDLINE
DN 97368343 PubMed ID: 9223338
TI Disruption of hippocampal development in vivo by **CR-50** mAb against reelin.
AU Nakajima K; Mikoshiba K; Miyata T; Kudo C; Ogawa M
CS Molecular Neurobiology Laboratory, Tsukuba Life Science Center, The Institute of Physical and Chemical Research (RIKEN), Tsukuba, Ibaraki 305, Japan.. nakjima@rtc.riken.go.jp
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Jul 22) 94 (15) 8196-201.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199708
ED Entered STN: 19970908
Last Updated on STN: 19970908
Entered Medline: 19970827

AB We previously generated a monoclonal alloantibody, **CR-50** , by immunizing reeler mutant mice with homogenates of normal embryonic brains. This antibody recently was shown to recognize a Reelin protein, which is coded by the recently identified candidate gene for the reeler mutation. However, it is still unclear whether Reelin, especially the **CR-50 epitope** region, is indeed responsible for the reeler phenotype in vivo. Here we show that Reelin is localized on Cajal-Retzius neurons in the hippocampus and that intraventricular injection of **CR-50** at the embryonic stage disrupts the organized development of the hippocampus in vivo, converting it to a reeler pattern. Labeling experiments with 5-bromodeoxyuridine demonstrated that the labeled cells in the stratum pyramidale of the **CR-50**-treated mice were distributed in a pattern similar to that of reeler. Thus, Cajal-Retzius neurons play a crucial function in hippocampus development, and the **CR-50 epitope** on Reelin plays a central role in this function.

L2 ANSWER 8 OF 8 MEDLINE

AN 97141547 MEDLINE
DN 97141547 PubMed ID: 8987733
TI Reelin is a secreted glycoprotein recognized by the **CR-50** monoclonal antibody.
AU D'Arcangelo G; Nakajima K; Miyata T; Ogawa M; Mikoshiba K; Curran T
CS Department of Developmental Neurobiology, St. Jude Children's Research Hospital, Memphis, Tennessee 38105, USA.
NC NSO9698 (NINDS)
P30CA21765 (NCI)
SO JOURNAL OF NEUROSCIENCE, (1997 Jan 1) 17 (1) 23-31.
Journal code: 8102140. ISSN: 0270-6474.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199702
ED Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970204
AB The neurological mouse mutant strain reeler displays abnormal laminar organization of several brain structures as a consequence of a defect in cell migration during neurodevelopment. This phenotype is a result of the disruption of reelin, a gene encoding a protein that has several structural characteristics of extracellular matrix proteins. To understand the molecular basis of the action of Reelin on neuronal migration, we constructed a full-length reelin clone and used it to direct Reelin expression. Here, we demonstrate that Reelin is a secreted glycoprotein and that a highly charged C-terminal region is essential for secretion. In addition, we demonstrate that an amino acid sequence present in the N-terminal region of Reelin contains an **epitope** that is recognized by the **CR-50** monoclonal antibody. **CR-50** was raised against an antigen expressed in normal mouse brain that is absent in reeler mice. The interaction of **CR-50** with its **epitope** leads to the disruption of neural cell aggregation in vitro. Here, we used **CR-50** to precipitate Reelin from reticulocyte extracts programmed with reelin mRNA, from cells transfected with reelin clones, and from cerebellar explants. The reelin gene product seems to function as an instructive signal in the regulation of neuronal migration.

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